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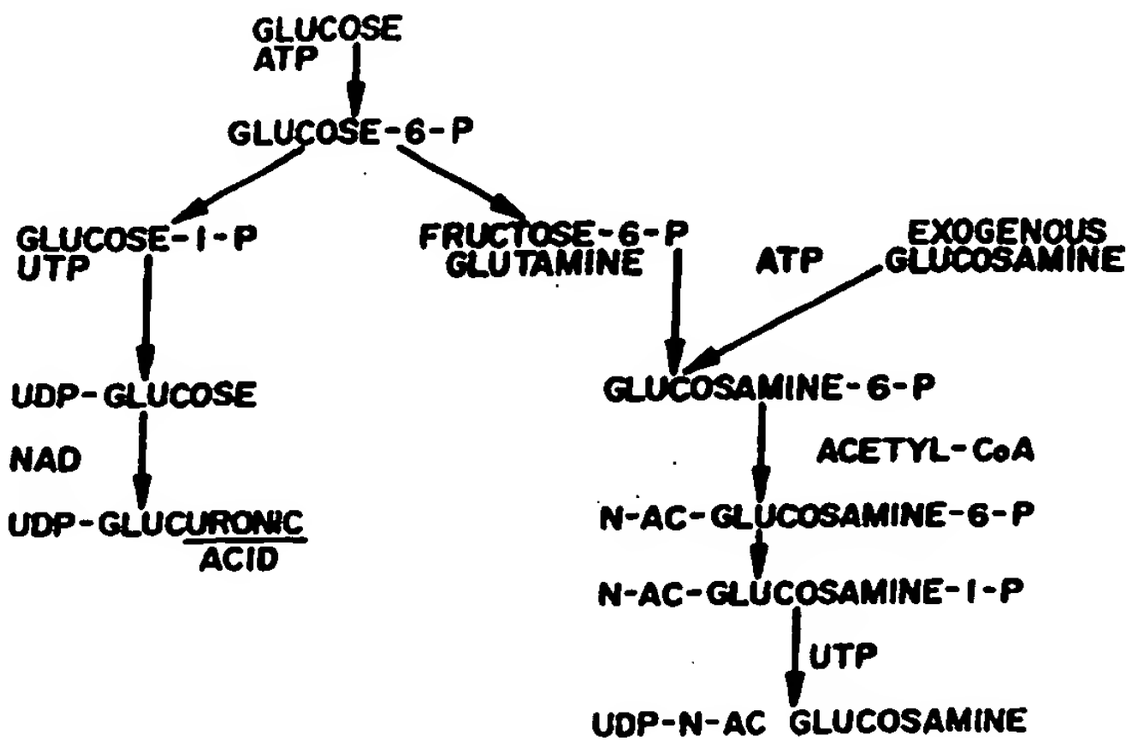

(57) Abstract

A composition for the protection, treatment and repair and for reducing the inflammation of connective tissue in mammals and a method for the protection, treatment of connective tissue in mammals by the administration of the composition. The composition includes at least two compounds selected from S–Adenosylmethionine (SAM), an aminosugar selected from the group consisting of glucosamine, glucosamine salts, glucosamine hydrochloride, galactosamine, N–acetylglucosamine, and fragments, mixtures or salts thereof, and a glycosaminoglycan or glycosaminoglycan–like compound selected from the group consisting of chondroitin, chondroitin salts, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, PPS, sodium PPS, calcium PPS, oversulfated GAGs, and fragments, salts, and mixtures thereof. The composition optionally includes manganese which promotes the production of connective tissue matrix. The composition also optionally includes methyl donors or methyl donor cofactors, such as vitamin B_{12}, vitamin B_6, folic acid, dimethylglycine or trimethylglycine, and betaine.

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AMINOSUGAR, GLYCOSAMINOGLYCAN OR GLYCOSAMINOGLYCAN-LIKE COMPOUNDS, AND S-ADENOSYLMETHIONINE

BACKGROUND OF THE INVENTION

Cross-Reference to Related Application

The present application is a continuation-in-part of co-pending United States Patent Application Serial No. 08/797,294, filed February 7, 1997, the disclosure of which is incorporated by reference herein in its entirety. That application is a continuation-in-part of U.S. Patent Application Serial No. 08/779,996 filed on December 23, 1996.

1. Field of the Invention

The present invention relates to compositions for the protection, treatment, repair and reduction of inflammation of connective tissue in humans and animals and, in particular, to compositions capable of promoting anti-inflammation, chondroprotection, chondromodulation, chondrostabilization, chondrometabolization and the repair and replacement of human and animal connective tissue.

2. Background of the Invention

The connective tissues of humans and animals are constantly subjected to stresses and strains from mechanical forces and from diseases that can result in afflictions, such as arthritis, joint inflammation and stiffness. Indeed, connective tissue afflictions are quite common, presently affecting millions of Americans. Further, such afflictions can be not only painful but, in their extreme, debilitating.

The treatment of connective tissue afflictions can be quite problematic. A simple decrease in the stress to which the connective tissue is subjected is often not an option,

especially in the case of athletes and animals such as race horses. Consequently, treatment is often directed at controlling the symptoms of the afflictions and not their causes, regardless of the stage of the degenerative process.

Presently, steroids, such as corticosteroids and NSAIDs, are widely used for the treatment of these ailments. [Vidal, et al., Pharmocol. Res. Commun., 10:557-569 (1978)]. However, drugs such as these, which inhibit the body's own natural healing processes, may lead to further deterioration of the connective tissue.

Connective tissue, for example articular cartilage, is naturally equipped to repair itself by manufacturing and remodeling prodigious amounts of collagen (a chief component of connective tissue such as cartilage) and proteoglycans (PGs) (the other major component of connective tissue such as cartilage). This ongoing process is placed under stress when an injury occurs. In such cases, the production of connective tissue matrix (collagen and PGs) can double or triple over normal levels, thereby increasing the demand for the building blocks of both collagens and proteoglycans.

The building blocks for collagen are amino acids, especially proline, glycine and lysine. PGs are large and complex macromolecules comprised mainly of long chains of modified sugars called glycosaminoglycans (GAGs) or mucopolysaccharides. The terms GAGs and mucopolysaccharides are understood in the art to be interchangeable. PGs provide the framework for collagen formation and also hold water to give flexibility, resiliency and resistance to compression.

Like almost every biosynthetic pathway in the body, the pathways by which both collagen and GAG form single molecule precursors are quite long. As is also characteristic of other biosynthetic pathways, the pathways by which collagen and GAGs are produced include what is called a rate-limiting step -- that is, one highly regulated control point beyond which there is a commitment to finish. The presence of such rate-limiting steps permits complicated

biosynthetic processes to be more easily and efficiently controlled by permitting the organism to focus on one point. For example, if conditions demand production and all the requisite raw materials are in place, then stimulation of the rate-limiting step will cause the end product to be produced. To stop or slow production, the organism needs simply to regulate the rate-limiting step.

In the production of PGs, the rate-limiting step is the conversion of glucose to glucosamine for the production of GAGs. Glucosamine, an aminosugar, is the key precursor to all the various modified sugars found in GAGs, including glucosamine sulfate, galactosamine, N-acetylglucosamine, etc. Glucosamine also makes up to 50% of hyaluronic acid -- the backbone of PGs -- on which other GAGs, like chondroitin sulfate are added. The GAGs are then used to build PGs and, eventually, connective tissue. Once glucosamine is formed, there is no turning away from the synthesis of GAG polymers.

Glucosamine has been shown to be rapidly absorbed into humans and animals after oral administration. A significant portion of the ingested glucosamine localizes to cartilage and joint tissues, where it remains for long periods. This indicates that oral administration of glucosamine reaches connective tissues, where glucosamine is incorporated into newly-synthesized connective tissue.

Glycosaminoglycans and collagen are the chief structural elements of all connective tissues. Their synthesis is essential for proper maintenance and repair of connective tissues. In vitro, the introduction of glucosamine has been demonstrated to increase the synthesis of collagen and glycosaminoglycans in fibroblasts, which is the first step in repair of connective tissues. In vivo, topical application of glucosamine has enhanced wound healing. Glucosamine has also exhibited reproducible improvement in symptoms and cartilage integrity in humans with osteoarthritis. [L. Bucci, Nutritional Supplement Advisor, (July 1992)].

The pathway for the production of proteoglycans may be briefly described as follows. Glucosamine is the main building block of connective tissue and may be provided either through the enzymatic conversion of glucose or through diet or external administration (see FIG. 1). Glucosamine may be converted into the other main component of connective tissue, namely PGs, upon incorporation of glucosamine into GAGs (see FIG. 2).

More specifically, GAGs are large complexes of polysaccharide chains associated with a small amount of protein. These compounds have the ability to bind large amounts of water, thereby producing a gel-like matrix that forms the body's ground substance. GAGs stabilize and support cellular and fibrous components of tissue while maintaining the water and salt balance of the body. The combination of insoluble protein and the ground substance forms connective tissue. For example, cartilage is rich in ground substance while tendon is composed primarily of fibers.

GAGs are long chains composed of repeating disaccharide units of monosaccharides (aminosugar-acidic sugar repeating units). The aminosugar is typically glucosamine or galactosamine. The aminosugar may also be sulfated. The acidic sugar may be D-glucuronic acid or L-iduronic acid. GAGs, with the exception of hyaluronic acid, are covalently bound to a protein, forming proteoglycan monomers. These PGs consist of a core protein to which linear carbohydrate chains formed of monosaccharides are attached. In cartilage proteoglycan, the species of GAGs include chondroitin sulfate and keratin sulfate. The proteoglycan monomers then associate with a molecule of hyaluronic acid to form PG aggregates. The association of the core protein to hyaluronic acid is stabilized by link proteins.

The polysaccharide chains are elongated by the sequential addition of acidic sugars and aminosugars, and the addition is catalyzed by a family of transferases. Aminosugars, such as glucosamine, are synthesized through a series of enzymatic reactions that convert glucose to glucosamine, or alternatively may be provided through the diet. The glucosamine is then

incorporated into the GAGs as described above. Acidic sugars may be provided through the diet, may be obtained through degradation of GAGs by degradative enzymes, or produced through the uronic acid pathway.

Since repeating disaccharide units contain one aminosugar (such as glucosamine), it is clear that the presence of an aminosugar in the production of connective tissue is important. Glucosamine is, by far, the more important ingredient in the production of connective tissue since it is the essential building block of GAGs. See FIG 1. GAGs contain hexosamine or uronic acid derivative products of the glucose pathway and from exogenous glucosamine, for example:

Hyaluronic acid	Glucosamine + Glucuronic Acid
Keretan-Sulfate	Glucosamine + Galactose
Chondroitin Sulfate	Glucuronic Acid + Galactosamine
Heparin Sulfate	Glucosamine + Glucuronic or Iduronic Acid
Heparan Sulfate	Glucosamine + Glucuronic or Iduronic Acid
Dermatin Sulfate	Iduronic Acid + Galactosamine

Chondroitin sulfate is a GAG that provides a further substrate for the synthesis of the proteoglycans. The provision of the chondroitin in its salt (e.g., sulfate) form facilitates its delivery and uptake by the humans and animals in the production of connective tissue. In addition, the sulfate portion of chondroitin sulfate is available for use in catalyzing the conversion of glucosamine to GAGs. Fragments of GAGs, including chondroitin sulfate, may also be used to provide a substrate for synthesis of proteoglycans since the assembly of PG occurs in the extracellular space.

In addition, chondroitin sulfate has been shown to have cardiovascular health benefits. [Morrison et al., Coronary Heart Disease and the Mucopolysaccharides (Glycosaminoglycans), pp. 109-127 (1973)]. Thus, the preferred form of glycosaminoglycan included in the compositions of the present invention is chondroitin sulfate or fragments thereof.

Chondroitin may be more efficacious than glucosamine for injury rehabilitation. [Christensen, Chiropractic Products, pp. 100-102 (April 1993)]. An evaluation of glucosamine

versus chondroitin for treatment of osteoarthritis has been conducted and concludes, contrary to Christensen, that glucosamine is preferred. [Murray, MPI's Dynamic Chiropractic, pp. 8-10 (September 12, 1993)]. Neither reference teaches or suggests combining the materials. Bucci (Townsend Letter for Doctors, pp. 52-54, January 1994), discloses the combination of glucosamine and chondroitin for treatment of osteoarthritis. Bucci has acknowledged that this combination was personally disclosed to him by one of the present inventors.

Chondroitin sulfate also acts to inhibit the degradative enzymes that break down connective tissue. In so doing, chondroitin sulfate promotes the maintenance of healthy connective tissues. When combined with glucosamine, which functions primarily as a building block for the synthesis of connective tissue, chondroitin sulfate works in concert with the glucosamine but may work in a different fashion. The ability of chondroitin sulfate to block degradation is one of its important functions.

GAGs may be semi-synthetic in that they may be chemically modified to contain more sulfur groups than in their initially extracted form. In addition, GAGs may be partially or completely synthesized, and therefore its building blocks (and, hence, the compound itself) may be of either plant or animal origin.

Pentosan polysulfate (PPS) is a compound that is understood to have anti-inflammatory activity, increase chondrocyte macromolecule biosynthesis resulting in increased cartilage matrix replacement, stimulate synovial fibroblast biosynthesis of hyaluronic acid, inhibit enzymes implicated in the degradation of cartilage matrix, mobilize thrombi and fibrin deposits in synovial tissues and subchondral blood vessels thereby increasing perfusion of the tissue, and mobilize lipids and cholesterol in synovial and subchondral blood vessels. As such, PPS is believed to accomplish many of the same functions as GAGs.

PPS is a semi-synthetic polysulfated xylan that is a sulfated form of a compound extracted from beechwood hemicellulose consisting of repeating units of (1-4) linked ß-D-

xylano-pyranoses. PPS is a low molecular weight linear polysaccharide, a semi-synthetic heparinoid that is considered an oversulfated form of a GAG.

There are several forms of PPS that display the above-described activities. Sodium PPS and a calcium-derived PPS (called CAPPS) may both be used to accomplish the functions of PPS. Each of these forms of PPS exhibit GAG-like activity, and will hereinafter be referred to as GAG-like compounds.

S-Adenosylmethionine (SAM) is a significant physiologic compound which is present throughout body tissue and takes part in a number of biologic reactions as a methyl group donor or as an enzymatic activator during the synthesis and metabolism of hormones, neurotransmitters, nucleic acids, phospholipids, and proteins. SAM may be second only to adenosine triphosphate (ATP) in the variety of reactions in which it is a cofactor. SAM is metabolized via three metabolic pathways of transmethylation, transsulfuration, and aminopropylation. [Stramentinoli, Am. J. Med., 83(5A):35-42 (1987)]. In higher organisms, SAM plays a significant role in transmethylation processes with more than 40 anabolic or catabolic reactions involving the transfer of the methyl group of SAM to substrates such as nucleic acids, proteins, and lipids, among others. Also, the release of the methyl group from SAM is the start of a "transsulfuration" pathway that produces all endogenous sulfur compounds. After donating its methyl group, SAM is converted into S-adenosylhomocysteine, which in turn is hydrolyzed to adenosine and homocysteine. The amino acid cysteine may then be produced from the homocysteine. The cysteine thus produced may exert a reducing effect by itself or as an active part of glutathione, which is a main cell anti-oxidant. [Stramentinoli, cited above].

SAM has been used to treat various disorders. In various forms of liver disease, SAM acts as an anticholestatic agent. [Adachi et al., Japan Arch. Inter. Med., 33:185-192 (1986)]. SAM has also been administered as an antidepressant for use in the management of psychiatric

disorders [Caruso et al., Lancet, 1: 904 (1984)], and as an anti-inflammatory compound in the management of osteoarthritis [Domljan et al., Int. J. Clin. Pharm. Toxicol., 27(7):329-333 (1989)].

Low levels of SAM are believed to play a role in reducing the risk of certain cancers. [Feo et al., Carcinogenesis, 6:1713-20 (1985)]. In addition, the administration of SAM has also been associated with a fall in the amount of early reversible nodules and the prevention of the development of late pre-neoplastic lesions and hepatocellular carcinomas. [Garcea et al., Carcinogenesis, 8:653-58 (1987)].

Unfortunately, SAM per se is unstable due to its high reactivity. The relatively recent synthesis of stable salts, however, has made SAM available for research and therapeutic use. [See, e.g., U.S. Patent Nos. 4,990,606 and 5,102,791].

SAM has been used outside of the United States in a number of clinical trials concerning the treatment of osteoarthritis. While used in these trials primarily as an analgesic and replacement for NSAID therapy, SAM is a precursor of polyamines. In addition to their analgesic and anti-inflammatory properties, and their ability to scavenge free radicals, polyamines may stabilize the polyanionic macromolecules of proteoglycans. [Schumacher, Am. J. Med., 83(5A):2 (1987)].

SAM may also function as a source of endogenous sulfur, which will increase sulfation of GAGs to be incorporated in proteoglycans. The inclusion of SAM is particularly beneficial in instances of subclinical deficiencies of SAM, occurring especially in elderly populations with higher risk of osteoarthritis [Frezza et al., Gastroenterol., 99:211-215 (1990)]. The supplementation of SAM may aid in instances of SAM deficiency where the ability of the body to sulfate GAGs may be compromised.

In addition, a number of metabolites of SAM aid in the repair of connective tissue, including glutathione, polyamines, methylthioadenosine, and adenosine. Glutathione works as

a scavenger of oxygen-related products [Shumacher, Am. J. Med., 83(Supp 5a):1-4 (1987); Matthew & Lewis, Pharmacol. (Life Sci. Adv.), 9:145-152 (1990); Szabo et al., Science, 214:200-202 (1981)] and thus has an anti-inflammatory effect. Polyamines, including spermine, spermidine, and putrescine, stabilize polyanionic macromolecules of proteoglycans [Schumacher, cited above; Conroy et al., Biochem. J., 162:347-350 (1977)] and thus protect proteolytic and glycolytic enzymes. These polyamines also have an anti-inflammatory effect [Bird et al., Agents Actions, 13:342-347 (1983); Oyangui, Agents Actions, 14:228-237 (1984)], probably as a scavenger of oxygen-related products [Kafy et al., Agents Actions, 18:555-559 (1986); Matthews & Lewis, cited above], and have an analgesic effect [Bird et al., cited above; Oyangui, cited above]. The SAM metabolite methylthioadenosine has a pronounced anti-inflammatory effect [Matthews & Lewis, 1990] while adenosine has a more modest anti-inflammatory effect [Matthews & Lewis, 1990].

Studies have shown that some forms of exogenous SAM are stable in digestive juices when given orally. [Stramentinoli et al., cited above; Vendemiale et al., Scand. J. Gastroenterol., 24:407-415 (1989)]. The metabolism of exogenous SAM appears to follow known pathways of endogenous SAM metabolism. [Kaye et al., Drugs, 40(Suppl. 3):124-138 (1990)]. In humans, oral SAM was tolerated to the same extent as placebo with very mild nonspecific side effects. [Schumacher, cited above; Frezza et al., cited above].

Manganese plays a role in the synthesis of GAGs, collagen and glycoproteins which are important constituents of cartilage and bone. Manganese is important for enzyme activity of glycosyltransferases. This family of enzymes is responsible for linking sugars together into glycosaminoglycans, adding sugars to other glycoproteins, adding sulfate to aminosugars, converting sugars into other modified sugars, and adding sugars to lipids. The enzymatic functions of glycosyltransferases are important in glycosaminoglycan synthesis (hyaluronic

acid, chondroitin sulfate, keratan sulfate, heparin sulfate and dermatin sulfate, etc.), collagen synthesis, and in the functions of many other glycoproteins and glycolipids.

Manganese also plays a role in the synthesis of glycosaminoglycans and glycoproteins, which are important constituents of cartilage and bone. Many reproductive problems in horses and skeletal abnormalities in foals have been ascribed to manganese deficiency. [Current Therapy in Equine Medicine, 2:402-403 (1987)].

Manganese deficiency leads to abnormal bone growth, swollen and enlarged joints, and slipped tendons in humans and animals. In humans, manganese deficiencies are also associated with bone loss and arthritis. Levels of all glycosaminoglycans are decreased in connective tissues during manganese deficiencies, with chondroitin sulfates being most depleted. Manganese-deficient organisms quickly normalize glycosaminoglycans and collagen synthesis when manganese is replenished.

Approximately 40% of dietary manganese is absorbed by the body tissue. Storage of manganese in the body is minimal -- a mere 12 to 20 mg is present in the body at any one time. Large amounts of calcium and phosphorus in the intestine are also known to interfere with manganese absorption. The richest dietary sources are the foods least consumed by the general public, such as whole grain cereals and breads, dried peas, beans and nuts. The ascorbate form of manganese is preferred due to the high bioavailability and the need for vitamin C (ascorbic acid) for collagen production. Vitamin C also enhances manganese uptake by the body.

Other optional ingredients in the compositions of the present invention are methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine. These ingredients augment the function of SAM in that they are cofactors in methylation or stimulate the production of endogenous SAM. [See, e.g., A. Barak et al., Alcoholism: Clin. and Exp. Res., 17(3):552-555 (1993)]. In addition, these compounds are likely to be lacking in patients suffering from connective tissue disorders. For example, it is

estimated that 12% of the elderly population in the United States suffers from a vitamin B_{12} deficiency, a group more likely to suffer from connective tissue disorders.

An adequate amount of vitamin B_{12}, for example, has an important environmental influence on the accumulation of homocysteine that results from the metabolism of SAM. In other words, methyl donors or methyl donor cofactors, such as vitamin B_{12} and the others listed in the preceding paragraph, can reduce levels of homocysteine when administered either alone or in combination.

Vitamin B_{12} is generally known to function as a coenzyme in biochemical reactions such as the synthesis of proprionic acid and of methionine. Recent evidence suggests that the elevated levels of plasma homocysteine increase the risk of occlusive vascular disease. Adequate amounts of vitamin B_{12} are considered the most important environmental influence on the accumulation of unnecessary homocysteine. [Joosten et al., Am. J. Clin. Nutr., 58(4): 468-76 (1993)]. In addition, it is also understood that vitamin B_{12} may play a role in the methylation of selenium. [Chen and Whanger, Tox. and Appl. Pharm., 118:65-72 (1993)]. Specifically, increased levels of vitamin B_{12} significantly contribute to selenium methylation and might decrease overall selenium toxicity by preventing its accumulation in tissues. [Chen and Whanger. cited above].

3. Description of Background Art

Several disclosures suggest provide exogenous quantities of glucosamine in order to bypass the rate-limiting step of the conversion of glucose to glucosamine in those pathways that produce PGs. For example, the intravenous administration of glucosamine (a precursor of the GAGs) and derivatives thereof has been disclosed in United States Patent No. 3,232,836, issued to Carlozzi et al., for assisting in the healing of wounds on the surface of the body. In United States Patent No. 3,682,076, issued to Rovati, the use of glucosamine and salts thereof is disclosed for the treatment of arthritic conditions. Finally, the use of glucosamine salts has also

been disclosed for the treatment of inflammatory diseases of the gastrointestinal tract in United States Patent No. 4,006,224 issued to Prudden. In vitro, glucosamine increases synthesis of collagen and glycosaminoglycans, the first step in repair of connective tissues, in fibroblasts. In vivo, topical application of glucosamine has enhanced wound healing.

Several disclosures also suggest going one step further in bypassing the glucose-to-glucosamine rate-limiting step, by providing exogenous quantities of various of the modified sugars found in the GAGs for producing proteoglycans. For example, in United States Patent No. 3,6797,652 issued to Rovati et al., the use of N-acetylglucosamine is disclosed for treating degenerative afflictions of the joints.

In still other disclosures of which we are aware, it has been taught to go still one step further in bypassing the glucose-to-glucosamine rate-limiting step by providing exogenous quantities of the GAGs themselves (with and without various of the modified sugars). For example, in United States Patent No. 3,371,012 issued to Furuhashi, a preservative is disclosed for eye graft material that includes galactose, N-acetylglucosamine (a modified sugar found in the GAGs) and chondroitin sulfate (a GAG). Additionally, United States Patent No. 4,486,416 issued to Soll et al., discloses a method of protecting corneal endothelial cells exposed to the trauma of intraocular lens implantation surgery by administering a prophylactically effective amount of chondroitin sulfate. Also, United States Patent No. 5,141,928 issued to Goldman discloses the prevention and treatment of eye injuries using glycosaminoglycan polysulfates.

United States Patent No. 4,983,580 issued to Gibson, discloses methods for enhancing the healing of corneal incisions. These methods include the application of a corneal motor composition of fibronectin, chondroitin sulfate and collagen to the incision.

In United States Patent No. 4,801,619 issued to Lindblad, the intraarticular administration of hyaluronic acid is disclosed for the treatment of progressive cartilage degeneration caused by proteoglycan degradation.

The use of PPS to treat connective tissue disorders is known. For example, it has been demonstrated that PPS, when administered intramuscularly at 10 mg/kg, is effective in prophylactically controlling proteoglycan loss and degradation of articular cartilage in arthritis model rabbits induced by immobilization of knee joints. [Golding and Ghosh, Current Therapeutic Res., 33:173-184 (1983)]. In humans, PPS has been shown to decrease pain during joint movement, increase range of motion, and decrease pain and fatigue when injected intramuscularly at a dosage of 100 mg approximately every other day for one month. [Engel, P. and Juhran, W. Arztl. Praxis., 34(51):2010 (1982)].

The use of a SAM and selenium composition as a nutritional supplement is disclosed in United States Patent Application Ser. No. 08/725,194 filed by one of the present inventors and is herein incorporated by reference. In addition, one of the inventors of the present invention has taught, in United States Patent No. 5,587,363 the combination of an aminosugar, such as glucosamine, and a glycosaminoglycan, such as chondroitin, for treatment of degenerative joint diseases. One of the present inventors has further taught the optional inclusion of manganese in a composition of an aminosugar and a glycosaminoglycan in United States Patent No. 5,364,845.

Accordingly, it can be seen that there remains a need for compositions which include analgesic, anti-inflammatory, and antidepressant components, as well as components that provide the building blocks for the production of connective tissue in humans and that also protect against the degradation of that tissue.

SUMMARY OF THE INVENTION

It is therefore an object of the present invention to provide a composition for the protection and repair and for reducing the inflammation of connective tissue in humans and animals.

It is a further object of the present invention to provide compositions which contain at least two compounds selected from the groups of S-Adenosylmethionine, an aminosugar, and a glycosaminoglycan or glycosaminoglycan-like compound, for facilitating the protection, treatment, repair and reducing the inflammation of connective tissue in humans and animals.

It is another object of the present invention to provide compositions which contain S-Adenosylmethionine and GAGs such as chondroitin salts and fragments thereof, or GAG-like compounds, such as PPS, sodium PPS, calcium PPS, for facilitating the protection, repair and for reducing the inflammation of connective tissue in humans and animals.

It is still a further object of the present invention to provide compositions which contain GAG-like compounds, such as PPS, sodium PPS, calcium PPS, and an aminosugar, such as glucosamine, for facilitating the protection, repair and for reducing the inflammation of connective tissue in humans and animals.

It is yet a further object of the present invention to provide compositions which contain S-Adenosylmethionine, an aminosugar or salts thereof, and GAGs or GAG-like compounds or fragments thereof for facilitating the protection, repair and for reducing the inflammation of connective tissue in humans and animals.

It is another object to optionally provide manganese to any of these compositions for humans and animals.

It is still a further object to optionally provide methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine, to any of these compositions of the present invention for humans and animals if desirable.

It is a further object of the present invention to provide methods of administering these compositions.

These and other objects of the present invention will become readily apparent from a reading of the following detailed description and examples.

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 is a sequence for the biosynthesis of hexosamines.

FIG. 2 is a schematic flowchart illustrating the biological pathway by which the composition of the present invention aids in protection and repair of connective tissue.

FIG. 3 is an enlarged portion of the flowchart of FIG. 2.

DETAILED DESCRIPTION OF THE INVENTION

According to the present invention, a composition containing at least two compounds selected from the group consisting of SAM, an aminosugar or salts thereof (e.g., glucosamine), and GAGs or GAG-like compounds (e.g., chondroitin salts, PPS, sodium PPS. or calcium PPS) or fragments thereof is provided to humans and animals for stimulating both collagen and PG synthesis and for reducing inflammation of connective tissue. Manganese, preferably manganese salts, may optionally be included to any of these compositions. In addition, other optional ingredients include methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine. These compositions may act to accomplish several functions, including bypassing the glucose to glucosamine rate-limiting step in the natural production of proteoglycans in humans and animals, and producing additional quantities of collagen and proteoglycans for use in the repair of damaged connective tissue. In addition. inflammation of connective tissue may be reduced by the compositions of the invention.. The compositions of the present invention may achieve these functions directly or through indirect pathways -- i.e., through their effect on other components in the living system which in turn can increase connective tissue synthesis or reduce inflammation.

The main components of the compositions of the present invention, (i.e., the aminosugar, GAG or GAG-like, and SAM components) are broadly defined herein, and the

scope of the present invention is intended to cover the components as herein defined and substantial equivalents thereto.

The aminosugar component of the compositions of the present invention may comprise natural, synthetic or semi-synthetic aminosugars including but not limited to glucosamine, glucosamine hydrochloride, galactosamine, glucosamine sulfate, N-acetylglucosamine and fragments, salts, and mixtures thereof. In addition, the term aminosugar is also used herein to encompass aminosugars that may have been chemically modified yet retain their function. Such chemical modifications include but are not limited to esterification, sulfation, polysulfation, acetylation, and methylation. Moreover, it is contemplated that the term aminosugar can extend to any composition of matter that is insubstantially different from the aminosugar as above-described.

The glycosaminoglycan ("GAG") component of the compositions of the present invention may comprise natural, synthetic or semisynthetic GAGs or GAG precursors, including but not limited to chondroitin, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, and fragments, salts, and mixtures thereof. In addition, the term GAG as used herein further encompasses GAGs that have been chemically altered yet retain their function. Such modifications include but are not limited to esterification, sulfation, polysulfation, and methylation. In fact, sulfated GAGs are a preferred component of the compositions of the present invention. Hence, mono-sulfated and polysulfated (or oversulfated) GAGs are preferred GAG components of the compositions of the present invention. The term GAGs also is intended to encompass alternative nomenclature for the same group of above-described compounds -- e.g., mucopolysaccharides, proteoglycans, and heparanoids. In addition, the GAG component of the compositions of the present invention may be derived from plant or animal sources, including but not limited to beechwood tree, to

forms of animal cartilage including shark cartilage, bovine trachea, whale septum. and porcine nostrils, and to mollusks such as Perna Canaliculus and sea cucumber.

Moreover, it is intended that the term GAG can extend to any composition of matter that is insubstantially different from the GAGs as above-described. An example of such a GAG-like compound that is within the scope of the present invention is pentosan polysulfate (PPS) as well as salts thereof such as calcium-derived PPS and sodium PPS. Accordingly, a preferred GAG-like compound that may be used in the compositions of the present invention is PPS.

The S-Adenosylmethionine ("SAM") component of the compositions of the present invention may comprise natural, synthetic or semi-synthetic SAM or SAM precursors, including but not limited to SAM and fragments, salts, and mixtures thereof. In addition, the term SAM as used herein further encompasses forms of SAM that have been chemically altered yet retain its function. Such modifications include but are not limited to esterification, sulfation, polysulfation, and methylation. Moreover, it is intended that the term SAM can extend to any composition of matter that is insubstantially different from the SAM as above-described that accomplishes the function of SAM -- i.e., functions as a methyl donor.

It is intended that the description of the preferred embodiments of the compositions of the present invention extend to encompass these definitions of the three main components. Thus, the following descriptions of the compositions of the present invention may refer to preferred components, but such descriptions do not limit the scope of the present invention, and it is intended that the broad range of components useful in the present invention are as defined above.

In one embodiment, a composition of the present invention include S-Adenosylmethionine (SAM) and an aminosugar, such as glucosamine, preferably in a salt form. In another embodiment of the present invention, the composition includes SAM and a glycosaminoglycan, such as chondroitin (preferably in a salt form such as chondroitin sulfate)

or a glycosaminoglycan-like compound, such as PPS, sodium PPS, and calcium PPS. In another embodiment, the composition of the present invention includes SAM, an aminosugar, such as glucosamine, preferably in a salt form, and a glycosaminoglycan such as chondroitin (preferably in a salt form, such as chondroitin sulfate) or a glycosaminoglycan-like compound, such as PPS, sodium PPS, and calcium PPS. In another preferred embodiment, the composition of the present invention includes an aminosugar, such as glucosamine (preferably in a salt form) and a glycosaminoglycan-like compound, such as PPS, sodium PPS, and calcium PPS.

Alternatively, fragments of a glycosaminoglycan or glycosaminoglycan-like compound may be used in a composition of the invention in addition to or in substitution for the glycosaminoglycan. Each of these compositions may optionally include manganese. A preferred form of manganese in such compositions is a manganese salt, such as manganese ascorbate, because the ascorbate is a soluble form of manganese which further provides ascorbic acid, a substance needed for collagen synthesis. Other manganese salts such, as for example, sulfate or gluconate, may be optionally used however. Each of these compositions may optionally contain one or more methyl donors or methyl donor cofactors selected from the group consisting of vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine.

Alternatively, two GAG or GAG-like compounds may be included in the compositions of the present invention is one is in sulfated form and the other is unsulfated. For example, it is contemplated that hyaluronic acid (an unsulfated GAG) and PPS may be combined to form a composition of the present invention. In fact, any of the GAGs or GAG-like compounds described above may be combined to form a composition of the present invention as long as one of the components is unsulfated hyaluronic acid.

Referring to FIGS. 2 and 3, the biosynthetic pathway for the production of connective tissue, which is affected by the method of the present invention by virtue of the components of

the composition of the present invention which aid in connective tissue repair, functions as described in the above background section of this application.

In a preferred embodiment, the aminosugar glucosamine is the base of the composition, providing the primary substrate for both collagen and proteoglycan synthesis. Glucosamine is the preferred substrate for proteoglycan synthesis, including chondroitin sulfates and hyaluronic acid. The glucosamine preferably is in a salt form so as to facilitate its delivery and uptake by humans and animals. The preferred salt forms are glucosamine hydrochloride, glucosamine sulfate and N-acetylglucosamine.

Administration of a preferred embodiment of the composition of the present invention provides the human or animal organism with exogenous quantities of SAM, an aminosugar or salts thereof, and a glycosaminoglycan or glycosaminoglycan-like compound or fragments thereof. If desired, the composition also provides the human or animal organism with exogenous quantities of manganese cofactors. Also if desired, the compositions of the present invention may include methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine.

The exogenous glucosamine provided by the composition of present invention is converted to proteoglycans as is seen in FIG. 2 and as described above.

In the former case, the glucosamine may be converted with the aid of manganese directly into GAG, including hyaluronic acid (which is 50% glucosamine and which forms the backbone of the proteoglycans). This core protein is then linked to the hyaluronic acid via the link protein, as is seen in FIG. 3.

In the latter case, the free amino acids are, with the aid of manganese and zinc cofactors (and ascorbic acid or vitamin C), converted to procollagen. The procollagen is then converted into collagen with the aid of copper or iron cofactors and vitamin C (ascorbic acid) and sulfate chelates.

Thus, preferred compositions of the present invention containing SAM and glucosamine advantageously stimulate the synthesis of collagen and glycosaminoglycans or mucopolysaccharides (GAGs), including hyaluronic acid, the backbone of proteoglycans (PGs), thereby providing a natural tissue repair function. These compositions provide the connective tissue repair function of glucosamine, the increased sulfation of GAGs by SAM, the stabilization by SAM metabolites of the polyanionic macromolecules of proteoglycans, and the additional analgesic, anti-inflammatory, and anti-depressant effects of SAM. The optional addition of manganese provides a further benefit if a deficiency of the mineral exists or if it is otherwise desired. The optional inclusion of methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine, helps to promote methylation and thereby convert homocysteine to methionine.

Another preferred composition of the invention comprises SAM and chondroitin salts (such as chondroitin sulfate) or PPS, sodium PPS, calcium PPS. SAM operates in this composition, in conjunction with endogenous glucosamine, as described above. Chondroitin salts, PPS. sodium PPS, and calcium PPS operate with SAM and endogenous glucosamine by inhibiting the synovial degradative enzymes. Chondroitin salts (such as chondroitin sulfate), PPS, sodium PPS, and calcium PPS also directly contribute to the pool of GAGs of cartilaginous tissue. Manganese salts may also be included in this composition in those cases where a deficiency of manganese exists. Methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine, may optionally be included in these compositions to help promote methylation and thereby convert homocysteine to methionine.

Another preferred embodiment of the composition of the present invention contains SAM, glucosamine, and chondroitin salts (such as chondroitin sulfate) or PPS, sodium PPS, and calcium PPS, and mixtures and fragments thereof, and also advantageously stimulates the

synthesis of collagen and glycosaminoglycans or mucopolysaccharides (GAGs), including hyaluronic acid, thereby providing a natural tissue repair function. This composition provides the superior connective tissue repair function of glucosamine, the above-described benefits of SAM, and the above-described benefits of chondroitin salts (including chondroitin sulfate), fragments of chondroitin salts, PPS, sodium PPS, and calcium PPS. Chondroitin salts (including chondroitin sulfate), PPS, sodium PPS, and calcium PPS also operate with SAM and glucosamine by inhibiting the synovial degradative enzymes. Chondroitin salts (including chondroitin sulfate), PPS, sodium PPS, and calcium PPS also directly contribute to the pool of GAGs of cartilaginous tissue. Manganese provides a further benefit if a deficiency of the mineral exists. As with the compositions described above, methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine, may optionally be included in these compositions to help promote methylation and thereby convert homocysteine to methionine. Tissue repair can thus be accomplished, in the context of the treatment and repair of connective tissue and the treatment of arthritic conditions, in almost all areas of the body both human and animal.

Another preferred embodiment of the composition of the claimed invention involves the combination of oversulfated GAGs or GAG-like compounds, such as PPS, sodium PPS, and calcium PPS, and an aminosugar, such as glucosamine. Each of these compounds functions as described above. The optional addition of manganese provides a further benefit if a deficiency of the mineral exists or if it is otherwise desired.

In the present method for the protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals, preferred compositions comprising amounts of SAM in combination with glucosamine including salts thereof in combination with chondroitin salts (including chondroitin sulfate), PPS, sodium PPS, and calcium PPS, or fragments thereof, or amounts of SAM and chondroitin salts (including chondroitin sulfate),

PPS, sodium PPS, and calcium PPS, or fragments thereof in combination with glucosamine including salts thereof, may be administered to humans and animals thereof. An additional preferred composition comprising amounts of SAM and chondroitin salts (including chondroitin sulfate), PPS, sodium PPS, and calcium PPS, or fragments thereof may be administered to humans and animals for stimulating proteoglycan synthesis and reducing inflammation. Manganese salts may also be optionally included in each composition in cases where a deficiency of manganese exists. Methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine, trimethylglycine, and betaine may optionally be included to these compositions as well.

The compositions of the present invention are administered to promote tissue repair, including cartilage repair, and the protection, treatment of arthritic conditions as well as connective tissue damage in humans and animals. The anti-depressant effect of SAM may help to alleviate the burden of sickness for some patients, thus enhancing their quality of life. This effect, as well as the analgesic and anti-inflammatory effects of SAM which will help alleviate the pain associated with arthritic conditions, may help remove impediments to physical activity. Increased levels of physical activity, in turn, can supply the loading and unloading forces necessary for the regeneration of articular cartilage. Supplementation with glucosamine, with its chondroprotective role, thus helps to ensure that the raw materials are available to support the increased regeneration of cartilage. The compositions of the present invention are also understood to play a chondromodulation, chondrostabilization, and chondrometabolizaton role.

The dosage of SAM in the nutritional supplements of the present invention ranges from about 5 mg to about 5,000 mg in humans and small animals, and from about 2 mg to about 20,000 mg in large animals (e.g., equine). The dosage of glucosamine in the nutritional supplements of the present invention ranges from about 50 mg to about 5,000 mg in humans and small animals, and from about 250 mg to about 40,000 mg in large animals (e.g., equine).

The dosage of chondroitin salts, PPS, sodium PPS, and calcium PPS in the nutritional supplements of the present invention ranges from about 15 mg to about 5,000 mg in humans and small animals, and from about 100 mg to about 30,000 mg in large animals. When included in the compositions of the present invention, manganese may optionally be present in the range of about 2 to about 75 mg in humans and small animals, and from about 10 mg to about 500 mg in large animals. The ascorbate component of the manganese ascorbate may range from about 10 mg to about 500 mg in humans and small animals, and from about 50 mg to about 2,500 mg in large animals. When included in the compositions of the present invention. the methyl donors or methyl donor cofactors, such as vitamins B_{12} and B_6, folic acid, dimethylglycine. trimethylglycine, and betaine may be present in the range of about 0.1 mg to about 5 g in humans and small animals, and from about 1 mg to about 50 g in large animals.

As a preferred embodiment, a dosage of the nutritional supplement composition of the present invention may consist of one or more capsules or tablets for human or small animal oral consumption. In such an embodiment, the preferred weight of the dosage is between about 5 mg to about 5,000 mg, and preferably about 2,500 mg. The dosage may be administered in a single daily dosage form in which all components are present, e.g., a capsule or tablet of preferably 2,500 mg. The dosage may also be administered in more than one dosage form in which each dosage form contains at least one component. When a single dosage is administered in more than one dosage form, the multiple dosage forms may be co-administered as a single dosage. Thus, for example, a single dosage may be comprised of a SAM dosage form co-administered with a glucosamine and chondroitin salts dosage form.

Alternatively, the nutritional supplement compositions of the present invention may be administered more than once daily. Hence, for example, the nutritional supplement compositions of the present invention may be in the form of an oral dosage form of 1250 mg administered twice daily or 833 mg administered three times daily. The number of daily

administrations will depend upon the needs of the human or animal recipient. Different connective tissue disorders and injuries require different amounts of the compositions of the present invention. In that regard, several dosages may be administered depending on the particular needs of the human or animal.

Alternatively, and of particular use in large animals, the compositions of the present invention may for example be administered in scoops. Such administration may take the form, for example, of a level scoopful containing about 1,800 mg glucosamine, about 600 mg chondroitin salts, about 16 mg of manganese (when included in the form of manganese ascorbate), and about 104 mg of ascorbate (when included in the form of manganese ascorbate).

These preparations may be made by conventional methods. For example, to prepare the compositions of the invention, the above-described ingredients are combined as the active ingredient in intimate admixture with a suitable carrier according to conventional compounding techniques. This carrier may take a wide variety of forms depending upon the form of preparation desired for administration, e.g., oral, injectable, sublingual, nasal, guttural, rectal, transdermal or parenteral.

In preparing the compositions in oral dosage form, any usual pharmaceutical medium may be employed. For oral liquid preparations (e.g., suspensions, elixirs, and solutions), media containing for example, water, oils, alcohols, flavoring agents, preservatives, coloring agents and the like may be used. Carriers such as starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents, and the like may be used to prepare oral solids (e.g., powders, capsules, pills, caplets, tablets, microencapsulated granules, microtablets, coated granules and lozenges). Capsules or tablets are a preferred oral dosage form. Controlled release forms may also be used. Because of their ease in administration, lozenges, tablets, pills, caplets, and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or

enteric coated by standard techniques. The compositions of the present invention may be in the form of one or more of these oral dosage forms -- i.e., a single dosage may be in multiple forms.

For parenteral products, the carrier will usually comprise sterile water, although other ingredients may be included, e.g., to aid solubility or for preservation purposes. Injectable suspensions may also be prepared, in which case appropriate liquid carriers, suspending agents, and the like may be employed.

Having discussed the composition of the present invention, it will be more clearly perceived and better understood from the following specific examples which are intended to provide examples of the preferred embodiments and do not limit the present invention. Moreover, as stated above, the preferred components described in these examples may be replaced by or supplemented with the any of the components of the compositions of the invention described above. Therefore, for example, the GAG component described in the example may comprise GAGs, modified GAGs such as oversulfated GAGs, or GAG-like compounds such as the various forms of PPS.

EXAMPLE 1

The composition of the present invention is made in one or more capsules for oral administration in humans and small animals. In a preferred embodiment, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
Chondroitin Sulfate	15-5,000 mg

EXAMPLE 2

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 1 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
Chondroitin Sulfate	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 3

For larger animals, such as horses, the composition of Example 1 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Chondroitin Sulfate	100-30,000 mg

EXAMPLE 4

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 3 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Chondroitin Sulfate	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 5

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg

EXAMPLE 6

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 5 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 7

For larger animals, such as horses, the composition of Example 5 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg

EXAMPLE 8

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 7 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 9

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Chondroitin Sulfate	15-5,000 mg

EXAMPLE 10

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 9 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Chondroitin Sulfate	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 11

For larger animals, such as horses, the composition of Example 10 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Chondroitin Sulfate	100-30,000 mg

EXAMPLE 12

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 11 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Chondroitin Sulfate	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 13

For those situations in which methyl donors or methyl donor cofactors are desired, such compounds may be added to the composition of Example 1 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg

Chondroitin Sulfate	15-5,000 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 14

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 13 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
Chondroitin Sulfate	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 15

For larger animals, such as horses, the composition of Example 13 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Chondroitin Sulfate	100-30,000 mg
vitamin B_{12}	1-100 mg

EXAMPLE 16

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 15 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Chondroitin Sulfate	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg
vitamin B_{12}	1-100 mg

EXAMPLE 17

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 18

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 17 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 19

For larger animals, such as horses, the composition of Example 17 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
vitamin B_{12}	1-100 mg

EXAMPLE 20

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 19 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
Manganese (as Ascorbate)	10-500 mg

Ascorbate (as Manganese Ascorbate)	50-2,500 mg
vitamin B_{12}	1-100 mg

EXAMPLE 21

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Chondroitin Sulfate	15-5,000 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 22

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 21 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Chondroitin Sulfate	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 23

For larger animals, such as horses, the composition of Example 21 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Chondroitin Sulfate	100-30,000 mg
vitamin B_{12}	1-100 mg

EXAMPLE 24

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 23 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Chondroitin Sulfate	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg
vitamin B_{12}	1-100 mg

EXAMPLE 25

The composition of the present invention is made in one or more capsules for oral administration in humans and small animals. In a preferred embodiment, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
PPS	15-5,000 mg

EXAMPLE 26

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 25 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
PPS	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 27

For larger animals, such as horses, the composition of Example 25 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
PPS	100-30,000 mg

EXAMPLE 28

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 27 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
PPS	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 29

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
PPS	15-5,000 mg

EXAMPLE 30

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 29 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
PPS	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 31

For larger animals, such as horses, the composition of Example 30 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
PPS	100-30,000 mg

EXAMPLE 32

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 31 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
PPS	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 33

For those situations in which methyl donors or methyl donor cofactors are desired. such compounds may be added to the composition of Example 29 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
PPS	15-5,000 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 34

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 33 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
PPS	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 35

For larger animals, such as horses, the composition of Example 33 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
PPS	100-30,000 mg
vitamin B_{12}	1-100 mg

EXAMPLE 36

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 35 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
PPS	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg
vitamin B_{12}	1-100 mg

EXAMPLE 37

For a further preferred composition, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
PPS	15-5,000 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 38

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 37 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
PPS	15-5,000 mg

Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg
vitamin B_{12}	0.1-10 mg

EXAMPLE 39

For larger animals, such as horses, the composition of Example 37 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
PPS	100-30.000 mg
vitamin B_{12}	1-100 mg

EXAMPLE 40

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 39 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
PPS	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg
vitamin B_{12}	1-100 mg

EXAMPLE 41

The composition of the present invention is made in one or more capsules for oral administration in humans and small animals. In a preferred embodiment, each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
hyaluronic acid	15-5,000 mg

EXAMPLE 42

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 41 so that each dosage contains:

Human & Small Animal	Range/Dose
SAM	5-5,000 mg
Glucosamine	50-5,000 mg
hyaluronic acid	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 43

For larger animals, such as horses, the composition of Example 41 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
hyaluronic acid	100-30,000 mg

EXAMPLE 44

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 43 so that each dosage contains:

Large Animal (Equine)	Range/Dose
SAM	2-20,000 mg
Glucosamine	250-40,000 mg
hyaluronic acid	100-30,000 mg
Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

EXAMPLE 45

The composition of the present invention is made in one or more capsules for oral administration in humans and small animals. In a preferred embodiment, each dosage contains:

Human & Small Animal	Range/Dose
Glucosamine	50-5,000 mg
hyaluronic acid	15-5,000 mg

EXAMPLE 46

For those situations in which manganese supplementation is desired, a manganese salt is added to the composition of Example 45 so that each dosage contains:

Human & Small Animal	Range/Dose
Glucosamine	50-5,000 mg
hyaluronic acid	15-5,000 mg
Manganese (as Ascorbate)	2-75 mg
Ascorbate (as Manganese Ascorbate)	10-500 mg

EXAMPLE 47

For larger animals, such as horses, the composition of Example 45 is administered as filled scoops.

Large Animal (Equine)	Range/Dose
Glucosamine	250-40,000 mg
hyaluronic acid	100-30,000 mg

EXAMPLE 48

For those situations in which manganese supplementation is desired, manganese salts may be added to the composition of Example 47 so that each dosage contains:

Large Animal (Equine)	Range/Dose
Glucosamine	250-40,000 mg
hyaluronic acid	100-30,000 mg

Manganese (as Ascorbate)	10-500 mg
Ascorbate (as Manganese Ascorbate)	50-2,500 mg

Many modifications may be made without departing from the basic spirit of the present invention. Accordingly, it will be appreciated by those skilled in the art that within the scope of the appended claims, the invention may be practiced other than has been specifically described herein. Hence, the attached claims are intended to cover the invention embodied in the claims and substantial equivalents thereto.

WHAT IS CLAIMED IS:

1. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising at least two compounds selected from the group consisting of an aminosugar selected from the group consisting of glucosamine, glucosamine hydrochloride, galactosamine, N-acetylglucosamine, and fragments, mixtures or salts thereof, S-Adenosylmethionine, and a glycosaminoglycan or glycosaminoglycan-like compound selected from the group consisting of chondroitin, chondroitin salts, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, PPS, sodium PPS, calcium PPS, oversulfated GAGs, and fragments, salts, and mixtures thereof.

2. The composition of claim 1, wherein a dose of the aminosugar, when present, ranges from about 50 mg to about 40,000 mg.

3. The composition of claim 2, wherein the dose of the aminosugar, when present, for humans and small animals ranges from about 50 mg to about 5,000 mg.

4. The composition of claim 2, wherein the dose of the aminosugar, when present, for large animals ranges from about 250 mg to about 40,000 mg.

5. The composition of claim 1, wherein a dose of the glycosaminoglycan or glycosaminoglycan-like compound, when present, ranges from about 15 mg to about 30,000 mg.

6. The composition of claim 5, wherein the dose of glycosaminoglycan or glycosaminoglycan-like compound, when present, for humans and small animals ranges from about 15 mg to about 5,000 mg.

7. The composition of claim 5, wherein the dose of glycosaminoglycan or glycosaminoglycan-like compound, when present, for large animals ranges from about 100 mg to about 30,000 mg.

8. The composition of claim 1, wherein a dose of the S-Adenosylmethionine, when present, ranges from about 2 mg to about 20,000 mg.

9. The composition of claim 8, wherein the dose of S-Adenosylmethionine, when present, for humans and small animals ranges from about 5 mg to about 5,000 mg.

10. The composition of claim 8, wherein the dose of S-Adenosylmethionine, when present, for large animals ranges from about 2 mg to about 20,000 mg.

11. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising two or more GAG or GAG-like compounds wherein at least one GAG is in sulfated form and at least one GAG is unsulfated.

12. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising: aminosugar selected from the group consisting of glucosamine, glucosamine salts, glucosamine hydrochloride, galactosamine, N-acetylglucosamine, and fragments, mixtures or salts thereof, in combination with S-Adenosylmethionine and a glycosaminoglycan or glycosaminoglycan-like compound selected from the group consisting of chondroitin, chondroitin salts, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, PPS, sodium PPS, calcium PPS, oversulfated GAGs, and fragments, salts, and mixtures thereof, wherein a dose of the aminosugar ranges from about 50 mg to about 40,000 mg, a dose of the

glycosaminoglycan or glycosaminoglycan-like compound ranges from about 15 mg to about 30,000 mg, and a dose of the S-Adenosylmethionine ranges from about 5 mg to about 40.000 mg.

13. The composition of claim 1, wherein the salt of glucosamine is selected from the group consisting of glucosamine hydrochloride, glucosamine sulfate, and N-acetylglucosamine.

14. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising: an aminosugar selected from the group consisting of glucosamine, glucosamine salts, glucosamine hydrochloride, galactosamine, N-acetylglucosamine, and fragments, mixtures or salts thereof, in combination with S-Adenosylmethionine.

15. The composition of claim 14, wherein a dose of the aminosugar ranges from about 50 mg to about 40,000 mg, and wherein a dose of the S-Adenosylmethionine ranges from about 2 mg to about 20,000 mg.

16. The composition of claim 14, wherein the dose of the aminosugar for humans and small animals ranges from about 50 mg to about 5,000 mg, and wherein the dose of S-Adenosylmethionine for humans and small animals ranges from about 5 mg to about 5,000 mg.

17. The composition of claim 14, wherein the dose of the aminosugar for large animals ranges from about 250 mg to about 40,000 mg, and wherein the dose of S-Adenosylmethionine for large animals ranges from about 2 mg to about 20,000 mg.

18. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising: a glycosaminoglycan or glycosaminoglycan-like compound selected from the group consisting of chondroitin,

chondroitin salts, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, PPS, sodium PPS, calcium PPS, and fragments, salts, and mixtures thereof in combination with S-Adenosylmethionine.

19. The composition of claim 18, wherein a dose of the glycosaminoglycan or glycosaminoglycan-like compound ranges from about 15 mg to about 30.000 mg, and wherein a dose of the S-Adenosylmethionine ranges from about 2 mg to about 20.000 mg.

20. The composition of claim 18, wherein the dose of the glycosaminoglycan or glycosaminoglycan-like compound for humans and small animals ranges from about 15 mg to about 5,000 mg, and wherein the dose of S-Adenosylmethionine for humans and small animals ranges from about 5 mg to about 5,000 mg.

21. The composition of claim 18, wherein the dose of the glycosaminoglycan or glycosaminoglycan-like compound for large animals ranges from about 100 mg to about 30,000 mg, and wherein the dose of S-Adenosylmethionine for large animals ranges from about 2 mg to about 20,000 mg.

22. A composition for protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising: a glycosaminoglycan or glycosaminoglycan-like compound selected from the group consisting of chondroitin, chondroitin salts, hyaluronic acid, glucaronic acid, iduronic acid, keratan sulfate, keratin sulfate, heparan sulfate, dermatin sulfate, PPS, sodium PPS, calcium PPS, oversulfated GAGs and fragments, salts, and mixtures thereof in combination with an aminosugar.

23. The composition of claim 22, wherein a dose of the glycosaminoglycan or glycosaminoglycan-like compound ranges from about 15 mg to about 30,000 mg, and wherein a dose of the aminosugar ranges from about 50 mg to about 40,000 mg.

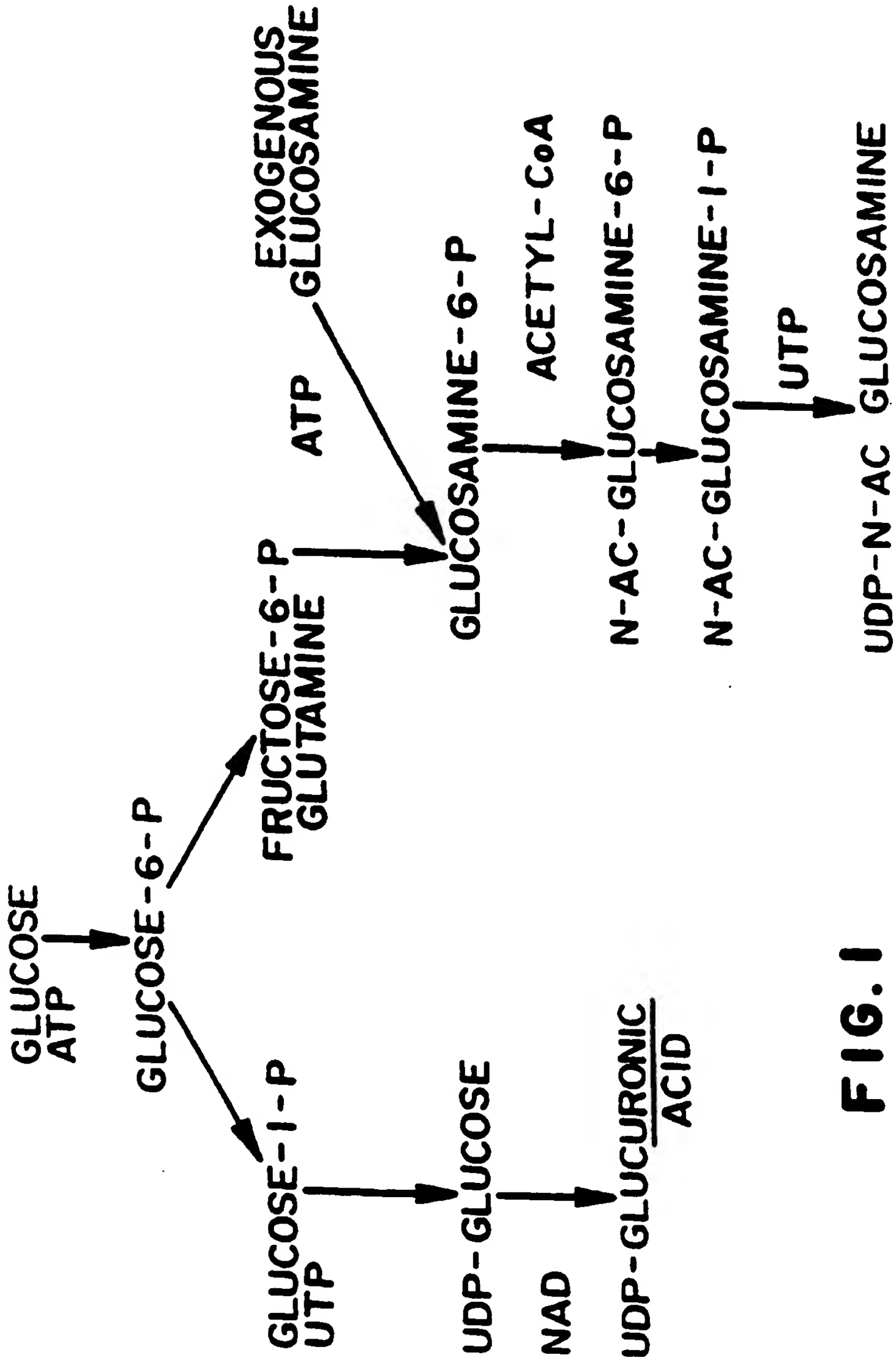
24. The composition of claim 22, wherein the dose of the glycosaminoglycan or glycosaminoglycan-like compound for humans and small animals ranges from about 15 mg to about 5,000 mg, and wherein the dose of aminosugar for humans and small animals ranges from about 50 mg to about 5,000 mg.

25. The composition of claim 22, wherein the dose of the glycosaminoglycan or glycosaminoglycan-like compound for large animals ranges from about 100 mg to about 30,000 mg, and wherein the dose of aminosugar for large animals ranges from about 250 mg to about 40,000 mg.

26. The composition of any of claims 1 through 25 further comprising manganese or a salt thereof.

27. The composition of any of claims 1 through 26 further comprising a methyl donor or methyl donor cofactor selected from the group consisting of vitamin B_{12}, vitamin B_6, folic acid, dimethylglycine, trimethylglycine, and betaine.

28. A method for the protection, treatment and repair and for reducing the inflammation of connective tissue in humans and animals comprising the step of administering any of the compositions of claim 1 to claim 27 to a human and an animal.


GLUCOSE
ATP
GLUCOSE-6-P
FRUCTOSE-6-P
GLUTAMINE
ATP
GLUCOSAMINE-6-P
ACETYL-CoA
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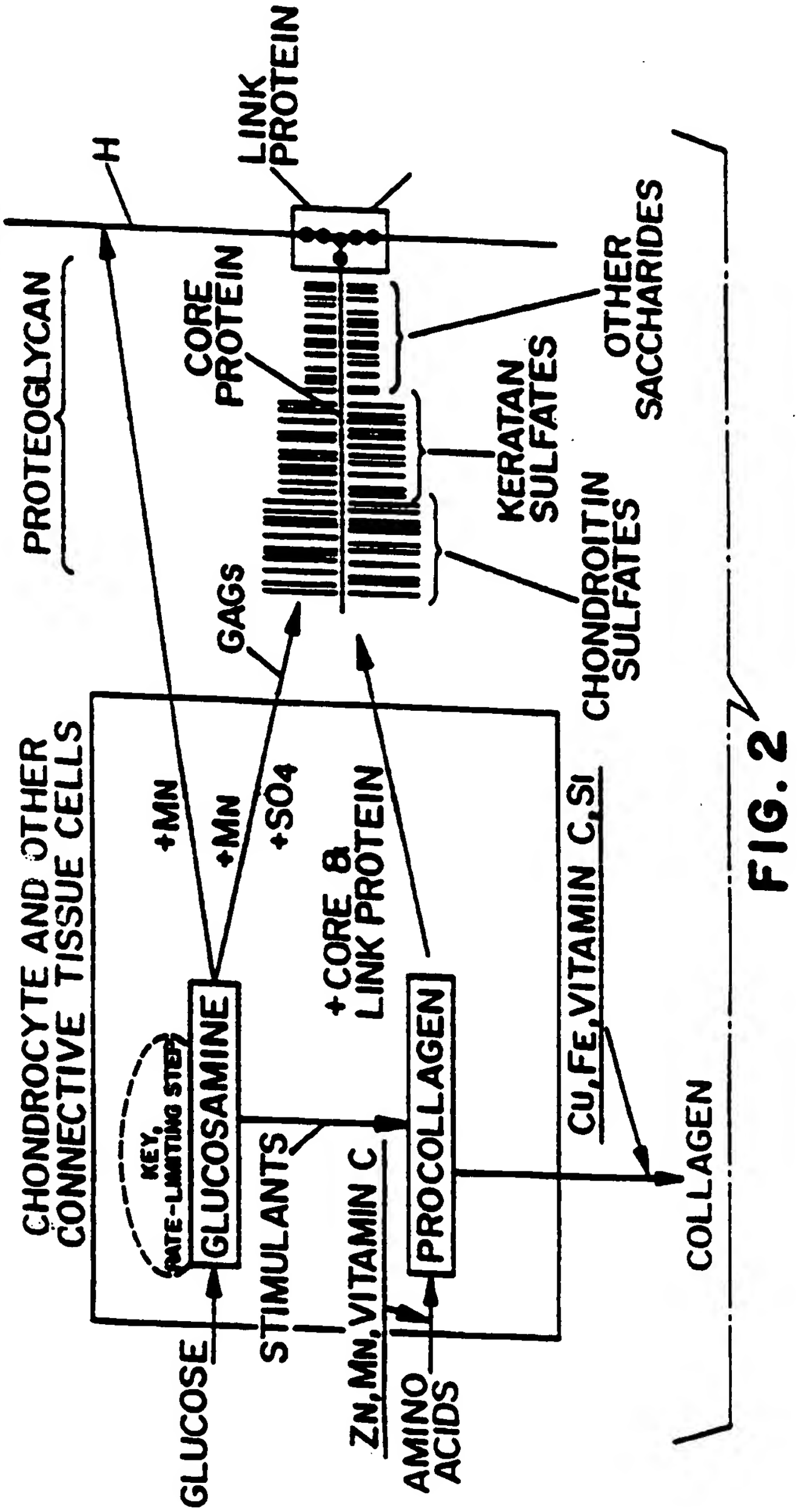
N-AC-GLUCOSAMINE-1-P
UTP
UDP-N-AC GLUCOSAMINE
GLUCOSE-1-P
UTP
UDP-GLUCOSE
NAD
UDP-GLUCURONIC ACID
EXOGENOUS GLUCOSAMINE

FIG. 1


HYALURONIC ACID
H
LINK PROTEIN
PROTEOGLYCAN
CORE PROTEIN
OTHER SACCHARIDES
KERATAN SULFATES
CHONDROITIN SULFATES
GAGS
+MN
+MN
+SO4
+CORE & LINK PROTEIN
CHONDROCYTE AND OTHER CONNECTIVE TISSUE CELLS
KEY, RATE-LIMITING STEP
GLUCOSAMINE
PROCOLLAGEN
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STIMULANTS
ZN,MN,VITAMIN C
GLUCOSE
AMINO ACIDS
COLLAGEN

FIG. 2

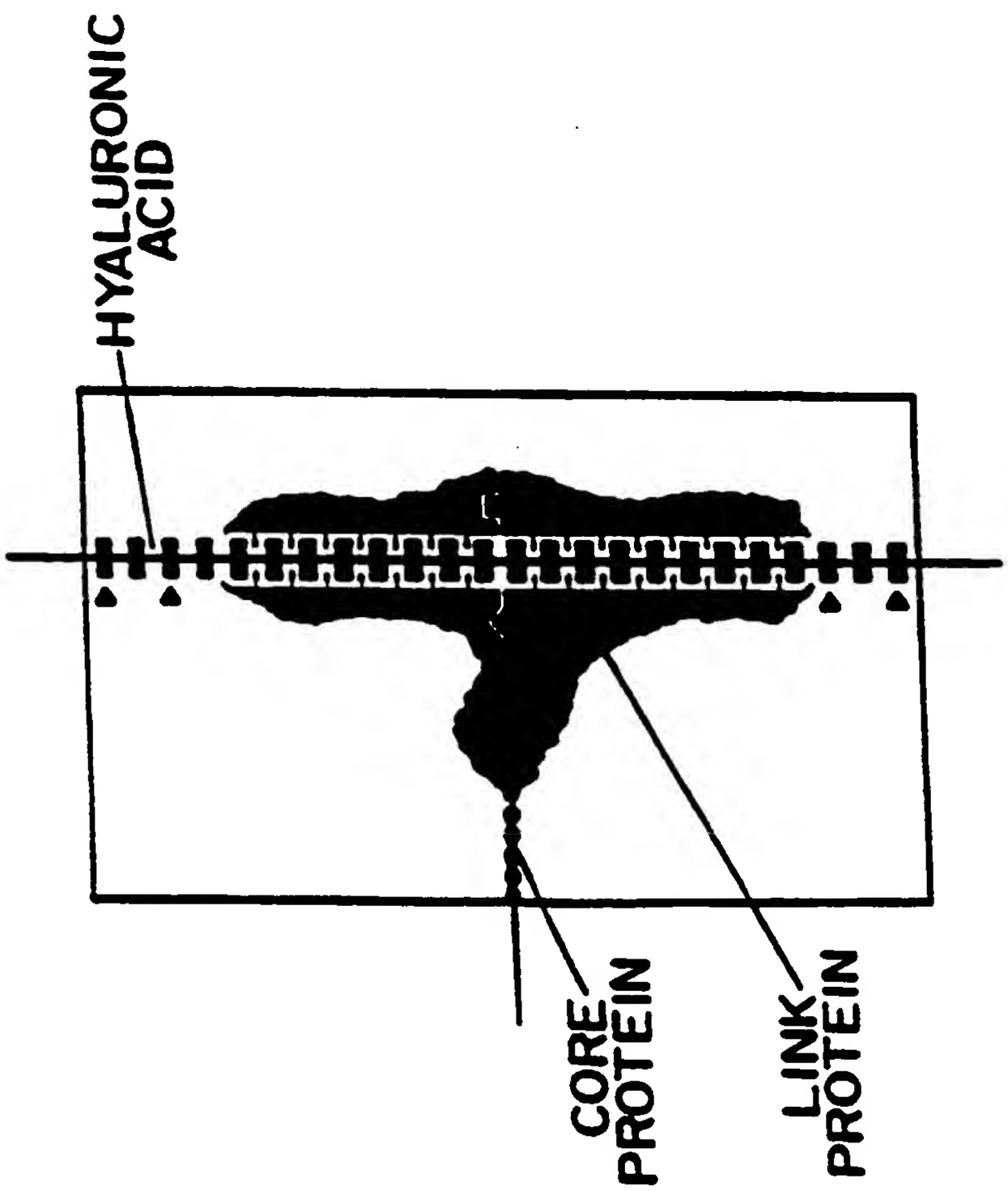

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07561

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/715, 31/70
US CL :514/54, 62
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/54, 62

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

APS- Files USPAT, USOCR, EPO & JPO

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, L ----- A	US 5,587,363 A (HENDERSON et al) 24 December 1996, col. 11, claims 1-8.	22-25 ---------- 1-21, 26

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 20 MAY 1998	Date of mailing of the international search report 08 JUL 1998
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer EVERETT WHITE Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)★

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US98/07561

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 27 and 28
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.